INFECTIONS IN RENAL TRANSPLANT RECIPIENTS

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CERTIFICATE

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INTRODUCTION

Advances in a wide variety of disciplines over the past 3 decades has made renal transplantation the most effective means of rehabilitating patients with end stage renal disease1. The transplantation of solid organs, initially an experimental act, has evolved with successful procedures that provide the best chance for survival and rehabilitation for hopelessly ill patients2. The first recorded Human renal transplant was performed by Joboulay Carrels teacher in 19063 using xenografts. The first human kidney allotransplant was carried out by the Soviet Surgeon Yu Yu Vorovoy in 19354.With the shortage of live organ donors, use of organs from cadaver became a viable alternative5. The results of cadaver transplant are improving progressively with the advent of cyclosporine and would shortly be comparable with that of live related donor transplant. As the availability of suitable cadaver kidneys does not match the requirement of all end stage renal failure patients6, live donor transplantation continues with the advent of lesser waiting period and fewer episodes of rejection.

In India, the first renal transplantation was done in the late 1960's by Sen et al in Bombay. Successful live related renal transplant programme was begun in CMC, Vellore in 1971. First free renal transplantation in a government hospital in South India was conducted by Prof. M.A.Muthusethupathi in Government Royapettah Hospital, Madras in 1981.

Infection and rejection, the two most important barriers to successful transplantation, are closely interwined, linked both by the immunosuppressive therapy required and by the similar array of cytokines, chemokines and growth factors elaborated during the course of both processes1. Any intervention that decreases the risk of rejection and permits the use of less intensive, immunosuppressive therapy will result in a decreased risk of life threatening infection. Any

intervention that decreases the risk of infection and permits the safe use of more intensive immunosuppressive therapy will decrease the risk of allograft loss from rejection. The inflammatory response to microbial invasion in the transplant patients often is attended by concomitant immunosuppressive therapy. As a result, not only are the signs and symptoms of infection frequently blunted, but traditional diagnostic approaches to infection such as skin testing and serologic testing are rendered significantly less sensitive7.

The complications encountered in renal transplant recipients treated with immunosuppressive drugs include variety of opportunistic infections8. The occurrence of infection in renal transplant recipients has been related to a number of clinical factors including patient's age, transplant type, HLA match, renal function, the occurrence of transplant rejection, the dosage of immunosuppressive therapy and neutropenia9.

As the life span of the immunocompromised patients has been extended, likewise the potential for exposure to nosocomial and opportunistic infections have increased. In comparison with the past however, more effective therapy in particular the antibiotics is now available to treat complications in immunocompromised patients. Thus the correct diagnosis of such condition is of utmost importance10.

Since isolation and identification of the real causative organism in infection in immunocompromised patient is mandatory, for saving the life of the patient, techniques which will confirmatively determine the real pathogen should be performed by proper collection avoiding contamination with normal flora to the maximal extent.

Advances in medical science including organ transplant have helped the less pathogenic organism to produce infection and infectious diseases are the commonest cause of morbidity and mortality in the renal transplant patients. Hence the causative agents of infection have to be analysed in detail, so that adequate treatment can be given at the appropriate time to save the patient's life.

AIM OF THE STUDY

- To study the infections in renal transplant recipients during the period Jan2004 to Dec 2005.

- To analyse the infectious episodes in relation to systems and the microorganisms involved.

- To study the infectious episodes relevant to post transplant follow up duration.

- To determine the in vitro susceptibility and resistance pattern of the bacterial isolates to different antimicrobial agents.

- To analyse the morbidity and mortality in renal transplant recipients due to infections.

REVIEW OF LITERATURE

Renal transplantation has become a well-established therapeutic option for end-stage renal disease, but infectious diseases remain a significant cause of morbidity and mortality11. Of the solid transplants, kidney transplantation is associated with the lowest rates of infections.In contrast to liver, heart, or lung allograft recipients, whose clinical status often detoriates before transplant, the elective or semielective nature of kidney transplantation along with anatomic considerations considerably lowers the risk of infection. Despite these considerations, infections in the renal transplant patient can cause significant morbidity , leading to graft dysfunction or systemic complications. Certain viruses such as *Cytomegalovirus, Ebstein barr virus* and *Hepatitis B* and *C* viruses can display an immunomodulating effect. This immunomodulation may contribute to allograft rejection, obliterative transplant arteriopathy, enhancement of other opportunistic infections, and development of post transplant lymphoproliferative disease (PLTD)12.

Infections are the major source of morbidity and mortality in renal transplant recipients. The risk of infection in organ transplant recipients, particularly opportunistic infections are largely determined by the interaction between two factors. The epidemiologic exposure the patients encounter and the patients net state of immunosuppression12.

Epidemiologic exposures of importance for the transplant patients can be divided into two categories – those occurring in the community and those occurring in the hospital. Community exposure of major concerns include - *Mycobacterium tuberculosis*, systemic mycosis (*Blastomycosis, Coccidiodomycosis, Histoplasmosis), Strongyloides Stercoralis, Hepatitis B and C,*

Human immunodeficiency virus, enteric bacterial pathogens (*Salmonella sp*) and *Influenza virus*1.

Two patterns of nosocomial exposure have been defined: domiciliary and non domiciliary. Domiciliary exposures occur in the room or ward where the patient is housed and are usually caused by contamination of the air or water supply by opportunistic pathogens.

Domiciliary outbreaks are characterized by clustering of cases in time and space and are relatively easily identified and controlled. Non domiciliary exposures are more problematic. These occur when patients are taken from their rooms to central facilities, such as the operating theatre, the radiology suite, or the cardiac catheterization laboratory. Non domiciliary exposures are more common within the hospital environment than domiciliary exposures and are more difficult to identify because of the frequent lack of clustering of cases1.

The net state of immunosuppression in transplant patients is a complex function determined by the interplay of a number of factors12

1. The prophylactic immunosuppressive protocol employed
2. Intensification of immunosuppression during episodes of rejection
3. The presence of neutropenia
4. Open wounds and foreign bodies(eg. Catheters)
5. Metabolic abnormalities (eg.., malnutrition, uremia, hyperglycemia)
6. Infection with immunomodulatory viruses.

CATEGORIES OF INFECTION OCCURING IN RENAL TRANSPLANT RECIPIENTS8

Infections related to technical complications

Transplantation of a contaminated allograft

Anastomotic leak or stenosis

Wound haematoma

Vascular access

Iatrogenic damage to the skin

Mismanagement of endotracheal tube leading to aspiration

Infection related to biliary, urinary and drainage catheters

Infections related to Excessive Epidemiologic Exposures

Nosocomial exposures (domiciliary and nondomiciliary)

Aspergillus sp

Legionella sp

Pseudomonas aeruginosa and other gram negative bacilli

Pneumocystis carinii

Exposures within the community

Systemic mycotic infections in certain geographic areas

Histoplasmosis capsulatum

Coccidioides immitis

Blastomyces dermatitidis

Strongyloides stercoralis

Opportunistic infection from environmental saprophytes

Cryptococcus neoformans

Aspergillus sp

Nocardia. asteroides

Pneumocystis carini

Respiratory infections circulating in the community

Mycobacterial tuberculosis

Influenza virus

Parainfluenza virus

Adenovirus

Respiratory syncytial virus

Infections acquired by ingestion of contaminated food or water

Salmonella sp

Listeria monocytogenes

Viral infection of Particular importance in Transplant Patients

Herpes group viruses

Hepatitis viruses

Papilloma viruses

Human immunodeficiency virus

In the post transplant period different infections occurs at different periods, the post transplant period is divided into 3 phases when evaluating the patient for possible infection.

1. Infections in the first one month transplant which is predominantly infection in allograft recipient prior to transplant is transmitted by contaminated allograft or infection related to surgical wound, IV lines and catheters. Because of this risk, potential donors are carefully evaluated for the presence of microbial infections that could contaminate the allograft.

2. Infections in 1 – 6 months post transplant: The causes of infection during this period are very different from those during the first month post transplant. By far the most important cause of infectious disease in this period are the immunomodulating viruses. For example, *Cytomegalovirus* by itself is the cause of more than two thirds of febrile episodes during this time. In addition to directly causing disease, these viruses combine with the sustained administration of immunosuppressive drugs to produce a greater net state of immunosuppression, a level that permits the occurrence of opportunistic infection due to organisms such as *Pneumocystis carinii, Listeria monocytogenes* and *Aspergillus fumigatus.*

3. Infections in the late period (more than 6 months post transplant).

Patients with functioning allograft on immunosuppressive therapy more than 6 months post

transplant can be divided into 3 groups.

a. Approximately 75% of these patients with a good allograft function are receiving minimal maintenance immunosuppressive agents and are free of chronic viral infections. The infections that these patients develop are similar to those observed in the general population – Influenza, Pneumococcal pneumonia, urinary tract infections etc

b. Approximately 10% to 15% have chronic viral infections with *Cytomegalovirus,Ebstein Barr virus, the Hepatitis viruses (HBV or HCV) or HIV* which inexorably lead to organ failure (chorioretinitis from *CMV* ,cirrhosis from *HBV or HCV*), malignancy (lymphoproliferative disease from *EBV,* hepatocellular carcinoma from *HBV* and possibly *HCV*; and possibly other viral associated malignancies such as squamous cell carcinoma from *papilloma virus*), or the acquired immunodeficiency syndrome (AIDS).

c. Finally 5% to 15% of patients who are characterized by relatively poor allograft function a history of acute or chronic rejection and an excessive amount of immunosuppression, are at highest risk of opportunistic infection such as those caused by *Cryptococcus neoformans, Pneumocystis carinii, Listeria monocytogenes* and *Nocardia asteroides*.

Death from infections may be a poor indicator of infection rate as infection may occur as a terminal event in persons dying due to other causes and since most of the infections can be successfully treated.

More than 80% of allograft recipients suffer atleast one episode of infection within the first transplant year[14]. Recipients at increased risk of infection include those who have leucopenia,

hyperglycaemia or azotemia and age more than forty[15]. In a study by Paterson et al from the University of Minnesota, 87% of the deaths were attributed to infection, 50% of which were viral in origin, 30% bacterial, 6% due to polymicrobial infection and 3% due to fungal infection[16].

URINARY TRACT INFECTIONS (UTI)

Urinary tract infections are most common form of bacterial infection among renal transplant recipients[13,27]. The reported incidence varies from 37 - 79%[17,18] and may account for more than 60% of bacteremia in these patients[19]. UTI is the most common complication in the first month after transplant and some reports indicate association of rejection with *Streptococcus fecalis* infection. Most cases involve gram negative organisms. Furthermore, most cases of gram-negative bacteremia in the transplant population began in the urinary tract. In a study by Takai et al (1998)[29], the majority of organisms cultured in UTI were gram-negative (76%), with approximately 1/3 being *Escherichia coli* and 1/5 being *Enterococcus and Klebsiella/Enterobacter*. The routine post transplant use of prophylactic antibiotics has reduced the frequency of UTIs to less than 10 % and essentially eliminates urosepsis unless urine flow is obstructed. Prophylaxis should start within a few days of transplant and continue for 3-6 months[12].

Postoperative foley tip cultures with subsequent development of UTI during the next two weeks was studied by Burleson et al(1977)[20]. None of the 15 patients with catheter tip negative cultures developed UTI. 16/24 with positive culture developed UTI within two weeks of removal of the catheter. None of the 16 patients had urine culture positive at the time of removal and so they concluded that catheterization is the source of many UTI post transplantation and catheter tip culture would be a useful guide in the management.

90% of the bacteria isolated from patients with UTI in post transplant period are gram negative

bacilli, most common being *E.coli*[21,22]. The other species include *Klebsiella, Proteus, Enterobacter* and *Pseudomonas*[23]. Most of the infection occurring in outpatient was discovered by frequent routine urine analysis and culture rather than by their symptoms. Most UTI are caused by single bacterial species. The isolation of three or more species in urine is usually contamination even when the colony count is high. A colony count threshold of $\geq 10^3$cfu/ml should be used to diagnose complicated UTI except when urine cultures are obtained through a catheter, in which a level of $\geq 10^2$cfu/ml is evidence of infection[102].

Urinary tract infections developing soon after transplantation are usually related to anatomical alteration resulting from surgery. Such early infections may require prolonged treatment. Urinary tract infections that occur more than 6 months after transplantation do not seem to be associated with the high rate of pyelonephritis or relapse seen with infections that occur in the first 3 months and may be treated for shorter periods.

In preventing UTI, Trimethoprim (80mg) and Sulfamethoxazole (400mg) may be used as prophylaxis 1 tablet at bed time for the first 4-6 months with nystatin orally thrice daily to prevent Candida infection during the antimicrobial prophylaxis[28].

RESPIRATORY TRACT INFECTION

Renal transplant patients have the respiratory infections that are common to normal persons and general hospital patients, but because of their defective cellular immunity, they also have infection by opportunistic organisms that in normal persons produce only trivial infection or not at all. Pneumonia is an important cause of morbidity and death in the transplant group[30]. The incidence of pulmonary infection in renal transplant recipients has declined from 25% to 8% with judicious use of immunosuppressive therapy and the aggressive treatment of infection[31].

MAJOR CAUSES OF PULMONARY INFECTION[30]

BACTERIA : *Pneumococcus*

Staphylococcus

Gram negative bacteria

Legionella

Nocardia

Mycobacteria

FUNGI : *Aspergillus sp*

Pneumocystis carinii

Candida sp

Mucor

Cryptococcus

VIRUSES : *Cytomegalovirus*

PARASITIC : *Strongyloides stercoralis*

Toxoplasma gondii

The problem of identifying the causative organism in lower respiratory tract infection is complicated by unreliability, questionable sensitivity and specificity of sputum gram stain and cultures[26,33].

Bronchoscopy with brush biopsy, bronchoalveolar lavage and transtracheal lung biopsy help in identifying the infective organisms in 90% of viral, 75% of P.carinii and 50% of Nocardial and fungal infections[34]. In open lung biopsy the diagnostic yield is 15% of the autopsy series even by the pathologist or microbiologist in patients with pulmonary infiltrates[36]. Chest x-ray alone is never diagnostic of any specific type of infection but it may give a clue as to the possible etiology and is helpful in assessing the progress of the disease and its response to therapy[37].

In a review of the spectrum of pulmonary infections in renal transplant recipients in the tropics by Kalra et al (2005)[39], 40 renal transplant recipients reported with 44 episodes of pulmonary infections. Out of 44 episodes of pulmonary infection evaluated, single causative organism could be found in only 24 (54.5%) episodes and multiple etiologies were found in 15 (34.1%) episodes. No definitive cause

could be found in 5 episodes. Out of 57 organisms isolated in the 44 episodes, 20 (45.4 %) were Bacteria, 16 (36.3 %) each were *M. tuberculosis* and Fungus, 3 were *CMV infection* and 2 were *Nocardia*. BAL gave a diagnostic yield of 75.8% (25 out of 33 cases). Nine of the forty patients died (mortality rate 22.5%) of which 6 deaths could be attributed directly to pulmonary infection. Out of these 9 patients who died, cause of pulmonary infection was Bacterial in 5, Fungal in 2 and *CMV disease* in 1. In one patient, organism could not be isolated.

The incidence of active tuberculosis infection in renal transplant recipient is variable from 0.45% - 3.64%[40]. Various forms of tuberculosis have been noted from cavitating to military form. Infection by *Mycobacterium tuberculosis* and *P.carinii* are the most common nonpyogenic infections in the first year after transplantation in developing countries. An aggressive search for tubercle bacilli should be made using bronchoscopy and examination of BAL fluid in patients not responding to a short trial of antibiotics. A four-drug regime without Rifampicin given for 18 months is effective for pulmonary tuberculosis in patients on cyclosporine. Routine prophylactic use of one single-strength tablet of Cotrimoxazole daily for at least six months after transplantation is recommended by Jha et al(1999)[41].

GASTROINTESTINAL TRACT INFECTION

Gastrointestinal complications are frequent in renal transplant recipients and can include oral lesions, esophagitis, peptic ulcer, diarrhea, colon disorders and malignancy. Oral lesions may be caused by drugs such as Cyclosporine and Sirolimus, by Virus or Fungal infections. *Candida* and *Herpes simplex* are the most common cause of Oesophagitis and stomatitis respectively in renal transplant recipients. Leukoplakia may develop in patients with *Epstein-Barr virus (EBV)* infection.

Candida is characterized by creamy white curd like patches on the tongue and on other mucosal surface, which are removable by scraping and leave a raw bleeding and painful surface. The patch is a pseudomembrane consisting of *Candida*, desquamated epithelial cells, leukocytes, ulceration, necrotic tissues and food debris[42]. Candida oesophagitis was believed to occur by direct spread from oral candida, but reports have shown that approximately 30% of the patient with candida oesophagitis have no associated Oral Candida[43]. The most common symptoms of Candida oesophagitis include painful swallowing, a feeling of obstruction on swallowing, substernal chest pain, nausea and vomiting. Definitive diagnosis was made by brushing or biopsy during endoscopy[44].

Gastroduodenal ulcers in renal transplant recipients are usually originated from excessive acid secretion or infection of *Helicobacter pylori.* However in a study by Abu Farsakh et al(2001)[45], prevalence of gastrointestinal symptoms due to *H.pylori* and endoscopic and histological findings in stable renal transplant recipients were similar to those in controls.

Helminthic infection in renal transplant recipient is not rare and hyper infestation with *Strongyloides stercoralis* has been noted[46]. Opportunistic infections with the nematode *Strongyloides stercoralis* occur most often in patients with impaired T lymphocyte function, including recipients of renal allografts. Occult intestinal infection can remain quiescent for more than 30 years, becoming apparent only after the initiation of immunosuppression. Pulmonary and gastrointestinal symptoms predominant as initial clinical manifestations in patients with Strongyloides hyperinfection or dissemination[47]. The diagnosis is usually made by identifying the larvae in stools of the patient coming from a endemic area.

Cryptosporidium is a coccidian protozoan causing enteritis in immunocompromised individuals. Involvement of the intestine is patchy with small intestine being the most commonly affected site. It presents as watery diarrhoea, crampy abdominal pain, weight loss, anorexia, flatulence and malaise. Incubation period for human cryptosporidiasis is between 2 to 14 days. Faecal examination reveals cryptosporidium oocysts and mucus but no blood or leucocytes. Cryptosporidial oocysts are acid fast, which help in their differentiation from yeast. The infection is self limiting[48].

Acute gastroenteritis in renal transplant recipients is caused by the same organisms seen in immunocompromised population. *Salmonella* infection are also found involving the gastrointestinal tract in transplant patients and they may require prolonged antibiotic therapy[49].

CENTRAL NERVOUS SYSTEM INFECTION

Infection of the central nervous system is an important cause of morbidity and mortality in the renal transplant recipient with a incidence of 7% with 50% mortality[50]. CNS infections in renal transplant recipients occur rather predictably between 1 and 12 months post transplant and are charaterised by a subacute onset and the frequent lack of systemic signs[30]. Organisms associated with CNS infection in renal transplant recipients in descending order of frequency are *Listeria, Cryptococcus, Mycobacteria, Aspergillus, Mucor, Toxoplasma* and *Strongyloides*[52].

The finding of disorientation, confusion, memory loss or a decreased level of consciousness in renal transplant recipient should lead to evaluation for a possible CNS infection. Two important diagnostic procedures are CT scan of the brain and lumbar puncture. *Listeria* usually occurs both in the early and late post transplant period. *Toxoplasma, Aspergillus and Nocardia* infections usually occurs within four months post transplant. *Mycobacterium tuberculosis and Cryptococcus infections* occur exclusively beyond four months post transplant.

BACTEREMIA

Bacteremia is a major cause of death in renal transplant recipients. The major cause of bacteremia in renal transplant recipient is Urinary tract infection with or without associated surgical complications. About 60 - 70% of the bacteremia in a study was found to have originated from the urinary tract[53]. With better approach to the treatment of infections, the incidence of bacteremias has decreased. Bowel perforation leading to gram negative bacteremia from the gastrointestinal tract is the other major cause[54].

Bacteremic infections are a major cause of death among organ transplant recipients. Death at 14 days after onset of bacteremia was 11% in kidney recipients. Risk of death is associated with the severity of the underlying condition of the transplant recipient, the source of the bacteremia, and the microbial agent. *Pseudomonas aeruginosa* and *Enterobacter* species had fatality rates of 47% and 63%[55].

After about one month post transplant, bacteremia without obvious evidence of septic foci or IV lines are most frequently due to *Listeria monocytogenes*[13]. The other organisms commonly isolated in bacteremic episodes are *Staph aureus, E.coli, P. aeruginosa and Candida*. In a study by lin et al (2001)[56], *E.coli* was the most common pathogen causing bacteremia (26.7%). Risk of death seemed higher if bacteremia occurred with a primary site of infection other than the urinary tract (26.7% vs 6.7 %) and after methyl prednisolone therapy.

SKIN AND SOFT TISSUE INFECTION

Skin infections among renal transplant recipients are very common and the spectrum of infections differs according to post transplant period[57].

Vesicular skin eruptions in renal transplant recipients are commonly due to *Varicella zoster (VZV) or Herpes simplex (HSV)* infection. Primary infection with *HSV* is rare in transplant patients. Reactivations are present, about 40% of which are asmptomatic. Warell et al (1986)[58] found that 47% of renal transplant recipients excreted *HSV*. There is no evidence of transmission of the infection by the grafted kidney, nor does it cause graft dysfunction.

Symptomatic HSV infection usually presents with labial and oral lesions in the first month after transplantation Two renal transplant recipients have been observed to have Eczema herpeticum (Koposis varicelliform eruption), a disseminated skin infection with *HSV* usually developing at sites of previous skin injury.Both the patients recovered without visceral dissemination in association with decrease in the level of immunosuppression[35].

Chickenpox is rare in graft recipients, but zoster occurs annually in approximately 3% of renal transplant patients,ten times the rate in normal people (Warrell et al., 1986)[58]. It may present as a typical localized dermatomal zoster, disseminated *VZV* infection or unilateral pain without skin eruption, associated with rise in specific antibody to *Varicellazoster*[59]. Zoster eruption may be more severe and last longer in transplant recipients than the normal people. Hence

the immune status of *VZV* in allograft recipients should be determined as a part of pretransplant work. The presence of VZV antibody by indirect fluorescent antibody test indicates immunity. Susceptible patients should be immunized in the pretransplant period with live attenuated vaccine. The vaccine appears to prevent clinical varicella following subsequent exposure. If an immunocompromised patient with no history of chicken pox or vaccination and with no detectable VZ antibody has had contact with Zoster or Chickenpox, Zoster immunoglobulin should be given as soon as possible[60].

Because of chronic immunosuppressive therapy, the skin of renal transplant recipients is considered more liable to fungal infections. In a study by Virgili et al (1999)[61], *Pityriasis versicolor (PV)* was the most frequent dermatomycosis and showed a higher prevalence than in the normal population. In a study by Thambiah et al (1999)[62], Dermatophytosis was detected in 42% of 100 renal transplant recipients screened, of whom 17% had the infection for more than 1 year. Tinea cruris and tinea corporis were the common clinical types observed. The commonest isolate was *Trichophyton rubrum*.

Chronic draining ulcer or nodular skin lesions should always raise the suspicion of atypical mycobacterial infection[63]. Musculoskeletal infections are caused by a variety of pathogens in renal transplant recipients. Apart from common bacterial organisms like *Staphylococci, Gram negative bacteria, Mycobacterium tuberculosis,* unusual organisms like atypical mycobacteria and fungi should be considered.

MALARIA

Malaria should be considered in the differential diagnosis of fever in transplant recipients who have received organs or blood products from an area of endemic malaria. Transfused blood is the presumed source of infection in the post transplant period. Mean incubation period is 12 days (7 – 29 days) for transfusion induced falciparum malaria. Falciparum malaria can stay in blood for three years. Transmission via the renal allograft is unlikely in live relative donor transplant who are malaria free during the pre and post transplant period. In a study of tropical infections after renal transplantation from the National kidney Institute, Phillipines, 5 episodes of proven malaria occurred in 440 patients who had undergone renal transplantation. The patient mortality was 40% in this group[64].

VIRAL HEPATITIS

The most important cause of Hepatitis in renal transplant recipients possibly is Non A Non B

Hepatitis65,66. Chronic Liver disease is one of the most important complications after renal transplantation. *Hepatitis B* and *Hepatitis C* are the main causes of liver disease. Although there are controversial results, in some series, *Hepatitis B* and *Hepatitis C* are associated with lower graft and patient survival. (Morelas et al, 2004)67. Despite the exclusion of patients with HBs Ag from organ and blood donation, the incidence of chronic liver disease after transplantation remained high, with abnormalities of liver function occurring in 7% to 24% of patients early in follow up and death due to liver failure in 8 % to 28% of the long term survivors of renal transplantation68.

The prevalence of HBV infection is higher in renal transplant recipients than in the general population, and HBV is a significant cause of mortality and morbidity after renal transplantation. (Emmet B. Keeffe, et al)69. Little clinical effects are seen in the early post transplantation period, but after two years, there is an increase in mortality in HBs Ag positive patients due to hepatic failure and intercurrent infection plays an important role in the mortality of these patients71. In a study by Behzad et al in Iran (2005)70, it was concluded that neither HBV nor HCV infection appears to cause or contribute to renal dysfunction in the early period (1 year) after renal transplantation. Nevertheless, a long-term consequence of chronic HBV or HCV liver disease or graft loss is not impossible in renal transplant recipients.

Transplantation of an organ from an HBV carrier is very efficient means of transmitting the virus13. The laboratory marker is the presence of *Hepatitis B* surface antigen. This prevalence of illness is unfortunate, because acquisition of HBV during transplantation is associated with a markedly increased risk of fulminant hepatitis71. More problematic is the allograft recipient who already is chronically infected with the virus. Although virus replication often decreases in the normal host, immunosuppressive therapy appears to directly stimulate viral replication. This effect is reflected in a prompt increase in Hepatitis viral DNA polymerase activity, HBe Ag and Hepatitis B virus DNA as

well as HBs Ag, that occurs shortly after initiation of immunosuppressive therapy.

Hepatitis C Virus, which accounts for virtually all cases of Non A Non B hepatitis in developed countries, is the major cause of hepatic and chronic liver disease in renal transplant recipients and might also be related to the development of Hepatocellular carcinoma8. Anti HCV antibodies have been reported for 10 % to 40% of renal transplant recipients. Patients with ESRD are at increased risk for HCV infection because of their continued exposure to blood and blood products, horizontal transmission within hemodialysis units52.

The presence of HCV infection greatly influenced graft survival in renal transplant patients and a higher proportion of infected patients had renal and Hepatic dysfunction. A significant increase in fatal chest infections was noted in HCV positive patients (Mitwalli et al, 2005)72.

In a study at Miami Veterans Hospital, Miami, the incidence of Anti HCV positivity pretransplant was 30%. At one year post transplant, 22% tested Anti HCV positive. 22% of the Anti HCV positive patients developed significant hepatitis post transplant. No chronic liver disease has been noted in them. No difference in the patient and graft survival were noted between Anti HCV positive and Anti HCV negative patients73.

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) is the most important viral infection affecting Renal transplant recipients[7]. In normal people, *CMV* infection uncommonly produces symptoms, but the virus subsequently becomes latent in monocytes, macrophages and polymorphonuclear leukocytes and tissues such as renal tubules. Cytomegaloviral infection in renal allograft recipients is more often symptomatic and can be severe or even fatal[30].

The infection is primary in a previously seronegative recipient. Primary infection occurs when the latently infected cells are transmitted from seropositive donors to seronegative recipients. Approximately 60% of the seronegative patients become symptomatic with CMV disease[74,75].

Secondary infection occurs in previously seropositive patients because of reactivation of the patient's own latent virus or reinfection, but it is not possible to distinguish clinically between these two possibilties[30]. It is currently estimated that approximately 20% of these individuals become symptomatic but this figure is strongly influenced by the immunosuppressive therapy being administered. The titre of neutralizing antibody present in seropositive individuals does not predict the occurrence of symptomatic disease or the gravity of clinical disease it develops[68].

Superinfection occurred when seropositive recipients receive an allograft from a seropositive donor and the reactivated virus is of donor rather than the recipient origin. The incidence of clinical disease in this group is probably 20% to 40% but again the incidence is modified by immunosuppressive therapy[77,78]. The most important infectious disease effect by CMV infection, however is it's broad based suppressive effect on host defences that can lead to opportunistic superinfection. Of particular interest is the linkage between *CMV* and *Pneumocystis* pneumonia[8,76].

WOUND INFECTION

The incidence of wound infection varies from 1.8% to 56%. Unrelated cadaver kidneys, diabetes, urinary fistulas and wound hematomas are all factors predisposing to wound infection. If wound infections secondary to haematoma and urinary fistula are excluded, the incidence is 1.6% in the University of Minnesota. If diabetics and retransplanted patients were excluded, the incidence of wound infection in non-diabetic patients who had their first transplant was only 0.7%, all being superficial[79].

When deep wound infection is suspected it should be aggressively evaluated with ultrasonography and CT scan. Fine needle aspiration under ultrasonography or CT scan guidance may be very useful in confirming the diagnosis and detecting the aetiological organism .The commonest infecting organism is either coliform bacteria or *Staphylococcus aureus*. Others are less common (Cohen,2001)[30].

Careful surgical technique and antibiotic prophylaxis can virtually eliminate the potentially grave complication of wound infection in this high risk group of patient[80]. Perioperative antibacterial administration can decrease the rate of

wound infection if it is above 4% without prophylaxis[81]. Such therapy should be against uropathogens and *Staphylococcus aureus*. The most important factor in the prevention of wound sepsis is the technical quality of the surgery performed.

MATERIALS AND METHODS

The study group comprised 88 cases of renal transplant recipients, who underwent renal transplantation for end stage renal failure (ESRF) at Government General Hospital, Chennai. It included two groups:

Group1 - 60 consecutive cases of renal transplantation performed on ESRF patients from Jan 2004 to Dec 2005 and including 59 live related donor kidney transplantation and 1 cadaver transplantation.

Group 2 - 28 renal transplant recipients who were transplanted before Jan 2004 and admitted for treatment during Jan 2004 to Dec 2005.

All renal transplant recipients were screened pre operatively for the presence of any overt or occult infection by

a. Urine culture

b. Ear ,Nose, throat, axilla, umbilicus, groin and vascular access swab culture

c. Serological test for infection with *Hepatitis B, Hepatitis C, Cytomegalovirus* and *Human immunodeficiency virus*.

d. X ray chest, ECG, Echocardiogram

e. HLA Typing of donor and recipient

POST OPERATIVE CARE

Immunosuppressive protocol consisted of administration of Triple drug regime - Cyclosporine,

Azathioprine and Prednisolone. Rejection episodes were treated with Intravenous Methylprednisolone, Intravenous Dexamethasone or Oral Prednisolone or OKT3.

Urine specimen were collected daily for analysis and cultured for the first two weeks. Drain fluid and tips of foley catheters were collected and cultured. Whenever infections occurred , samples were collected accordingly.

Patients were immunized against Hepatitis B whenever possible.

The transplant protocol followed at Government General Hospital,Chennai is as follows

- ESRF patients with voluntary living related donor are accepted for renal transplantation.
- Second degree relatives are accepted only if there were no suitable first degree donor available.
- Cadaver transplant
- All recipients receive a minimum of 3 units of non specific blood transfusion.
- All patients were started on Triple drug regime - Cyclosporine, Azathioprine and Prednisolone.
- Details of pre transplant, intraoperative and post transplant events were carefully recorded.
- Recipients discharged from the hospital on 14th post operative day unless delayed by complications. Outpatient follow up done at weekly intervals for months and at two

weekly intervals thereafter and more frequently if required.

All patients were put on Oral Cotrimoxazole prophylaxis for three months post transplant and Nystatin mouth wash.

Bacterial, Fungal, Viral and Parasite studies were carried out on the specimens whenever required.

METHODOLOGY

A. Collection of specimen

B. Macroscopical examination

C. Microscopical examination

D. Culture procedure and identification of organisms

E. Antibiogram

F. Detection of Extended spectrum beta lactamase (ESBL) production.

G. Plasmid DNA isolation for Gram negative bacteria that were resistant to Third generation cephalosporins.

A. COLLECTION OF SPECIMENS

Urine, Drain fluid, foley catheter tip and Drain tip were collected from all cases. According to signs and symptoms, Blood, Serum, Sputum, Oral scrapings, Faeces, Pus and CSF were collected.

1. Urinary tract

(a) Urine

1. Urine from the catheterized individuals were collected in a sterile universal container.

2. Clean catch mid stream urine were collected in a sterile wide mouthed bottle after thorough preliminary cleaning of external genitalia with soap and water.

(b) Catheter tips - were put in glucose broth.

2. Respiratory system

(a) Sputum - patients were instructed to have mouth wash and gargle with sterile distilled water and to cough when the sputum was felt in the throat / mouth. Patient was instructed to collect it directly into a sterile container at one time.

(b) Bronchoalveolar lavage - Under sterile precautions, bronchoalveoalar lavage was done and sample collected in two sterile tubes.

(c) Pleural fluid - under sterile precautions, the aspirated pleural fluid was collected in a sterile tube.

3. Gastrointestinal tract

(a) Oral scraping - The lesions were scraped with sterile swab.

(b) Upper gastrointestinal brushing - were collected in a sterile test tube.

(c) Gastric aspirate - Gastric aspiration was done and the sample was collected in a sterile tube.

(d) Faeces - the specimens were collected in a sterile 25 ml wide mouthed bottles.

4. Central nervous system

Cerebrospinal fluid - Under sterile aseptic condition, lumbar puncture was done and the CSF was collected in a sterile test tube.

5. Skin and soft tissue

(a) Wound swab - using sterile swab, the specimen's were collected.

(b) Pus - using sterile swab or sterile syringe the specimen's were collected in sterile tubes.

(c) Tissue biopsy - under sterile aseptic condition, the tissue biopsy was taken and collected in sterile tubes.

6. Drain

(a) Drain fluid were collected in a sterile test tube.

(b) Drain tips were put in glucose broth.

7. Bacteremia

(a) Blood - Under sterile aseptic conditions, 5 ml of blood was taken intravenously and inoculated into Brain heart infusion broth immediately.

(b) Serum - Serum samples were collected in sterile test tubes for Widal test and Microscopic agglutination test (MAT).

8. Malaria – Peripheral blood samples on clean glass slides were taken.

9. Hepatitis B, Hepatitis C and Cytomegalovirus - serum samples were collected in a sterile test tube.

The Samples were transported to the laboratory immediately without any delay and processed.

B. MACROSCOPIC EXAMINATION

1. Urine - observed for turbidity and color

2. Sputum - Examined for color (red, Brown, Yellow, Green or Whitish), Consistency - thick or thin sputum, Presence of mucous, mucopurulent and frothy material (saliva) and any other abnormal looking material.

3. Bronchoalveolar lavage - observed for blood and abnormal materials.

4. Cerebrospinal fluid - Examined for turbidity, contamination with blood (from the puncture site) and color.

5. Faeces - Looked for consistency, presence of mucous, pus, blood and presence of parasites.

C. MICROSCOPICAL EXAMINATION

(a) Urine (1) Wet preparation - examined for the presence of pus cells, red cells, yeast cells and bacteria.

(2) Gram stain - smear was prepared, air dried and fixed. Stained by Grams method and examined under oil immersion and looked for gram positive and gram negative bacteria.

(b) Sputum (1) Wet preparation - the sputum was mixed with a drop of saline, looked for cells and yeast like organisms.

(2) KOH mount- The sputum was emulsified with few drops of 10 % KOH kept for 5 minutes and examined under low and high power objective for the presence of branching and unbranching fungal elements.

(3) Stained preparation

Gram stain – smear was prepared, air dried and fixed. Stained by grams method and examined under oil immersion and observed for the presence of squamous, epithelial cells, cellular infiltrates - polymorphonuclear leukocytes, mononuclear leucocytes, gram positive and gram negative bacteria.

Ziehl - Neelson technique - smears were stained by Ziehl - Neelson technique and examined for acid fast bacilli.

(c) Bronchoalveolar lavage (1) Direct wet preparation and KOH mount was done, under the low and high power objective, looked for the presence of pus cells, mononuclear cells, ciliated columnar epithelial cells, yeast like organisms and fungal elements.

(2) Stained preparation - Two smears were air dried and fixed.

- One smear was stained by gram's technique and examined for cells, bacteria and fungi.

- Second smear was stained by Ziehl – Neelson technique and examined for acid fast bacilli.

(d) Pleural fluid - Two smears were prepared - one for gram's stain and one for Ziehl – Neelson technique and examined.

(e) Gastric lavage - Smear prepared by Ziehl – Neelson technique was examined for acid fast bacilli.

(f) Faeces - examined for the parasites by saline and iodine mount.

(g) Cerebrospinal fluid - Two smears were made air dried and fixed, Gram stain and Ziehl Neelson stain were done and observed under oil immersion.

Negative staining – India Ink preparation – one drop of CSF was placed on a clean glass slide and mixed with a drop of India ink and a cover slip was placed, examined under low and high objective for the organisms. Staining by Nigrosin method was also done.

(h) Malarial parasites - Thick and thin blood smear was prepared, stained by Leishman's stain and examined for malarial parasites.

CULTURE MEDIA USED

Specimen	Media used		
	Enrichment	**Bacterial culture**	**Fungal culture**
Urine	-	CLED	SDA
Catheter tips	Glucose broth S/ C, after 24 hrs	MAC,BAP	SDA
Sputum		MAC,BAP,CAP,LJ	SDA
Broncho alveolar Lavage		MAC,BAP,LJ	SDA
Pleural fluid		MAC,BAP,LJ	SDA
Oral scraping	-	-	SDA
Oesophageal brushing	-	-	SDA
Gastric lavage	-	LJ	-
Faeces	Selenite broth S/ C after 6hrs	MAC BAP	-
Wound swab/Pus		MAC BAP	SDA
Tissue biopsy	Glucose broth S/C after 24 hrs SD broth S/C after 24 hrs	MAC BAP LJ	SDA
CSF		MAC,BAP,CAP	SDA

BAP - Blood agar plate
LJ - Lowenstein Jensen medium
CLED - Cystine Lactose Electrolyte Deficient Medium
MAC - Mac conkey agar
SDA - Sabouraud's Dextrose Agar
CAP - Chocolate agar

D. CULTURE PROCEDURE AND ISOLATION OF ORGANISMS.

The specimens were inoculated into their respective media immediately without delay.

(a) Incubation of inoculated media -

MAC, BAP and CLED plates were incubated aerobically at 370C. Chocolate agar plates was incubated in a candle jar at 370C.

LJ slopes - one was inoculated at room temperature and other in the incubator at 370C.

Sabourauds dextrose agar slant's - one incubated at 370C aerobically and another one incubated aerobically at 250C.

(b) Examination of inoculated media

After 24 hrs incubation

MAC, BAP, Chocolate agar, CLED plates were examined after 24 hrs for the presence of growth. If growth was seen, the degree of growth was noted as profuse, moderate or scanty. Preliminary identification of organism was made by colony morphology using hand lens. In case of mixed growth, the relative degree of growth of each species was noted. The growth was subjected to Grams stain, Hanging drop for motility and biochemical reactions for identification of the organism. If no growth occurred or no colony suggestive of possible pathogens were seen., the plates were reincubated for another 24 hrs.

For urine culture - inoculation was done by using a standard bacteriological loop. Colony count of $\geq$ 103 indicates significant bacteriuria.

After 48 hrs incubation, MAC, BAP, Chocolate agar, CLED plates were examined for the presence of growth. The growth was subjected to Gram's stain, Hanging drop for motility and biochemical reactions for identification of organism.

If no growth was seen, plates were discarded and reported as no growth.

LJ media were examined daily for the first 5 days and then at weekly intervals for upto 3 months.

The Sabouraud's dextrose agar slants were observed for the presence of growth daily. If positive for growth, smear was prepared and stained by Gram's stain, Lactophenol cotton blue mount was done and examined. If yeast cells were seen, germ tube test was done to differentiate Candida albicans from the other Candida species. If no growth was present, the SDA slants were reincubated further and examined on 3rd, 5th, 7th, 10th, 14th, 21st days and one month. If no growth was seen after one month, then the SDA slants were discarded. CHROM agar medium was inoculated for speciation of Candida.

Serological tests - Widal test for Enteric fever.

MAT for Leptospirosis

Hepatitis B, Hepatitis C, Cytomegalovirus - The serum samples were screened for the presence of Hepatitis B surface antigen, Anti HCV antibody (Microlisa Kit, J. Mitra) and CMV IgM by ELISA (Lilac kit) technique.

E. ANTIBIOGRAM

Antibiotic susceptibility testing of the bacterial isolates were done by Disc diffusion technique using Mueller Hinton agar plates and the susceptibility or resistance of the isolates were noted by Kirby Bauer chart and recorded. The antibiotics used for Antibiotic susceptibility testing were Penicillin, Erythromycin, Ampicillin, Cefotaxime, Ofloxacin, Co trimoxazole, Oxacillin and Vancomycin for gram positive bacteria.

Gram negative bacteria were tested with Gentamycin, Ofloxacin, Cefuroxime, Ceftazidime, Cefaperazone, Ampicillin, Co trimoxazole and Imipenem.

F. DETECTION OF ESBL PRODUCTION

Gram negative bacilli that was resistant to ceftazidime was tested for Extended spectrum beta lactamase production. ESBL production was tested with ceftazidime and amoxyclav discs. Extension of amoxyclav zone towards ceftazidime was taken as positive for ESBL production.

MIC for Ceftazidime was put as per NCCLS standards for the Gram negative isolates that were resistant to Third generation cephalosporin Ceftazidime.

G. PLASMID DNA ISOLATION

Plasmid DNA isolation was done for Ceftazidime resistant Gram negative bacteria.

RESULTS

Total Number of patients - 88

TABLE – 1

Group 1	60 renal transplant recipients during Jan 2004 to Dec 2005
Group 2	28 renal transplant recipients, transplanted before Jan 2004 and admitted for treatment during Jan 2004 to Dec 2005

TABLE 2
Age and Sex distribution

Age	Sex	
	Male	**Female**
10-20	14	10
21-30	33	6
31-40	20	2
41-50	2	-
51-60	1	-
Total	**70 (79.55%)**	**18(20.45%)**

Predominant Age group was between 21 - 40 yrs and 80% were males.

DONOR STATUS

Live Donor Transplantation - 87

Cadaver transplantation - 1

Sex distribution in relation to infections.

TABLE 3

No. of patient	Male	Female
	70	**18**
Total no. of infections (n=246)	189	57
%	76.8	23.2

Higher incidence of infection occurred in Male patients.

Prevalence of infection in renal transplant recipients

TABLE 4

Infections	No. of Infections (n = 246)	
Urinary tract infection	130	52.8%
Respiratory tract infection	27	10.3%
Drain infection	23	9.3%
Gastrointestinal tract infection	17	6.9%
Bacteremia	11	4.4%
Skin and soft tissue infection	10	4%
Cytomegalovirus	8	3.2%
Wound infection	6	2.4%
Hepatitis C	5	2.03%
Malaria	4	1.6%
Hepatitis B	4	1.6%
Central nervous system infection	1	0.4%

Urinary tract infections were common followed by Respiratory tract infections.

Isolation of organisms in relation to the infection involved

TABLE - 5

Infections	Bacteria	Fungus	Virus	Parasite	Total (n = 246)
Urinary tract infection	114	16	-	-	130
Respiratory tract infection	22	5	-	-	27
Drain infection	19	4	-	-	23
GIT infection	-	12	-	5	17
Bacteremia	11	-	-	-	11
Skin and soft tissue infection	6	4	-	-	10
Hepatitis B & C	-	-	9	-	9
CMV infection	-	-	8	-	8
Wound infection	5	1	-	-	6
Malarial infection	-	-	-	4	4
CNS infection	-	1	-	-	1
	177	**43**	**17**	**9**	**246**

Bacterial infections were the most common infections in the post transplant period.

URINARY TRACT INFECTIONS

Total no. of infections : 130

Total no.of patients : 60

Multiple episodes of infection - 45 patients

Single episode of infection - 15 patients

Sex distribution

TABLE - 6

No. of Patient	Male	Female
	48	**12**
Total no. of infection	98	32
%	75.3	24.7

Increased incidence of urinary tract infections were noted in Males.

Organisms isolated (n=130)

TABLE - 7

Bacteria – 114 (87.6%)			**Fungus -16 (12.4%)**
E.coli	45	39.4%	
Klebsiella pneumoniae	24	21%	
Pseudomonas aeruginosa	23	20.1%	*Candida albicans* - 13 (81.2%)
Proteus mirabilis	10	8.7%	
Staph aureus	4	3.5%	*Candida krusei* - 2 (12.5%)
Klebsiella oxytoca	4	3.5%	
Acinetobacter baumanii	2	1.7%	*Candida tropicalis* - 1 (6.2%)
Enterococci	2	1.7%	

Commonest organism causing UTI was *E.coli* (39.4%)

Isolation of organisms in relation to duration of post transplant period

TABLE – 8

Month	Bacteria	Fungus	Total
0 – 1	86	6	92
2 – 3	12	8	20
4 – 6	5	0	5
7 – 12	2	0	2
> 12	9	2	11

More number of bacterial infections occurred during 1st month post transplant

RESPIRATORY SYSTEM (RTI)

Total no. of infections = 27

Total no of patients = 22

Sex Distribution

TABLE-9

	Male	Female
No. of Patients	**20**	**2**
Total no. of infection	24	3
%	88.8	11.2

Higher incidence of RTI occured in Males.

Organisms isolated (n=27)

TABLE -10

Bacteria -22 (81.4%)		**Fungus - 5 (18.6%)**	
Klebsiella pneumoniae	10	*Aspergillus flavus*	2
M. tuberculosis	6	*Candida albicans*	1
Pseudomonas aeruginosa	4	*Aspergillus fumigatus*	1
Staph. aureus	2	*Mucor*	1

Isolation of Organisms in relation to post transplant period.
TABLE - 11

Month	Mycobacteria	Other Bacteria	Fungus
0 – 1	0	1	0
2 – 3	0	2	0
4 – 6	4	6	1
7 – 12	2	3	2

> 12	0	4	2

Bacterial infections were common during the first one year post transplant period.

DRAIN INFECTIONS

Total no. of infections - 23

Organisms isolated (n=23)

TABLE -12

Bacteria – 19 (82.6%)		**Fungus – 4(17.3%)**
Pseudomonas aeruginosa	8	*Candida albicans* - 4
E.coli	4	
Staph aureus	3	
Klebsiella pneumoniae	3	
Micrococci	1	

Pseudomonas aeruginosa was the predominant organism causing drain infection.

GASTROINTESTINAL TRACT INFECTION (GIT)

Total no. of infections – 17

Organisms isolated (n=17)

TABLE – 13

Fungus -12 (70.5%)		**Parasite- 5 (29.5%)**	
Candida albicans	10	*E. h cyst*	3
Candida tropicalis	1	*A. duodenale*	1
Candida glabrata	1	*S. stercoralis*	1

Isolation of Organisms in relation to post transplant period

TABLE – 14

Months	Fungus	Parasite
0 -1	2	0
2 -3	2	3
4 -6	4	1
7 - 12	1	0
> 12	3	1

Most of the GIT infections occurred during 2 – 4 months post transplant.

Candidiasis

TABLE – 15

Oral candidiasis	5
Oesophageal candidiasis	3
Oral and Oesophageal candidiasis	2+2

Candida albicans was the common organism causing GIT infection.

BACTEREMIA

Total no. of bacteremia – 11

TABLE – 16

Organisms	**No. of infection**
Klebsiella pnuemoniae	4
Pseudomonas aeruginosa	2
E. coli	2
Acinetobacter baumanii	1
Staph aureus	1
Leptospira icterohaemorrhagia	1

Klebsiella pnuemoniae was the most common organism causing Bacteremia.

SKIN AND SOFT TISSUE INFECTION

Total no. of infections – 10

Organisms isolated

TABLE - 17

Bacteria 6 (60%)		**Fungus 4 (40%)**	
Staph aureus	2	*Trichophyton rubrum*	2
E. coli	2	*Trichophyton mentagrophytes*	1
Pseudomonas aeruginosa	1	*Aspergillus flavus*	1
M.tuberculosis	1		

CYTOMEGALOVIRUS INFECTION

Total no of CMV positive - 8

Before 12 months - 5

After 12 months - 3

CMV infection occurred more commonly within one year post transplant period.

VIRAL HEPATITIS

TABLE – 18

Virus	No of infections n=9
Hepatitis C	5
Hepatitis B	4

Hepatitis C

No. of Hepatitis C positive - 5

TABLE - 19

Month	No. of infections
0 – 1 yr	1
> 1 yr	4

Hepatitis B

No. of Hepatitis B positive - 4

TABLE - 20

Month	No. of infections
0 – 1	-
2 – 3	-
4 – 6	1
7 – 12	1
> 12	2

Hepatitis B and *C* occurred more commonly after 1 year post transplant.

WOUND INFECTION

Total no. of infection – 6

Organisms isolated

TABLE – 21

Bacterial (5)		**Fungus (1)**
Klebsiella pneumoniae	2	*Candida albicans* - 1
E. coli	2	
Staph aureus	1	

Wound infections caused by bacteria occurred more commonly in the first month post transplant period.

Malaria

No. of infection - 4

Plasmodium falciparum - 2

Plasmodium vivax - 2

CENTRAL NERVOUS SYSTEM INFECTION

Cryptococcus neoformans – 1

(isolated in the 9th month post transplant period)

ISOLATION OF ORGANISMS IN RELATION TO DURATION OF POST TRANSPLANT PERIOD

TABLE - 22

Months	**Bacteria**	**Mycobacteria**	**Fungus**	**Virus**	**Parasite**

0 - 1	113	0	13	0	2
2 – 3	19	0	10	0	3
4 -6	14	4	5	4	2
7 - 12	7	2	7	5	1
> 12	17	1	8	8	1

SYSTEM WISE ISOLATION OF ORGANISMS IN RELATION TO POST TRANSPLANT DURATION.

TABLE - 23

Months	UTI	RTI	Drain	GIT	Bacteremia	Skin/soft tissue	CMV	Hepatitis	Wound	Malaria	CNS
0 -1	92	1	23	2	1	1	-	-	6	2	-
2– 3	20	2	-	5	3	2	-	-	-	-	-
4– 6	5	11	-	5	2	1	2	2	-	1	-
7- 12	2	7	-	1	2	3	3	2	-	1	1
> 12	11	6	-	4	3	3	3	5	-	-	-

MORTALITY

TABLE – 24

No. of patients	Mortality
88	10

Out of 10 deaths, 4 were due to Bacteremia (40%).

Mortality was more commonly due to Gram negative bacteria.

ANTIBIOGRAM

ANTIBIOTIC SENSITIVITY FOR GRAM POSITIVE ORGANISMS

TABLE - 25

Organism	Pen %	Ery %	Oxa %	Oflox %	Ampi %	Co-tri %	Cefotax %	Vanco %
Staph aureus (13)	1 (7.6)	10 (76.9)	11 (84.6)	9 (69.2)	6 (46.1)	3 (37.5)	8 (61.5)	13 (100)
Enterococci faecalis (2)	0	1 (50)	0	0	1 (50)	0	0	2 (100)
Micrococci (1)	0	1 (100)	0	1 (100)	0	0	0	1 (100)

Gram positive organisms showed Highest sensitivity to Vancomycin followed by Erythromycin.

2 Oxacillin resistant Staph aureus (MRSA) were sensitive to Vancomycin.

ANTIBIOTIC SENSITIVITY FOR GRAM NEGATIVE ORGANISMS

TABLE 26

Organism	Oflox %	Genta %	Ampi %	Co- tri %	Cefurox %	Ceftaz %	Cefaper %	Imi %
E.coli (53)	49 (92)	21 (39.6)	42 (79.2)	38 (71.6)	30 (56.6)	51 (96.2)	51 (96.2)	53 (100)
Klebsiella sp (47)	39 (82.9)	40 (85.1)	4 (8.5)	31 (81.5)	40 (85.1)	47 (100)	47 (100)	47 (100)
Pseudomonas aeruginosa (38)	10 (26.3)	24 (63.1)	4 (10.5)	6 (15.7)	0	25 (65.7)	25 (65.7)	38 (100)
Proteus mirabilis (10)	10 (100)	8 (80)	10 (100)	2 (20)	4 (40)	10 (100)	10 (100)	10 (100)
Acinetobacter baumanii (3)	3 (100)	3 (100)	1 (33.3)	1 (33.3)	0	3 (100)	3 (100)	3 (100)

No. of Organisms resistant to Ceftazidime : 15 (2 *E.coli* & 13 *Pseudomonas aeruginosa*)

No. of ESBL producers : 11(2 *E.coli* & 9 *Pseudomonas aeruginosa*)

Plasmid Isolation: Plasmid was isolated in 8 *Pseudomonas aeruginosa* isolates

ISOLATION OF ORGANISMS IN RELATION TO THE SITE OF INFECTION

TABLE - 27

ORGANISMS	Urine	Sputum/ BAL/ Pleural fluid	Drain	Blood	Skin/ Soft tissue	Wound	Oral scraping / Faeces/ Gastric aspirate	CSF
BACTERIA								
E.coli	45	-	4	2	2	2	-	-
Klebsiella pneumoniae	24	10	3	4	-	2	-	-
Pseudomonas aeruginosa	23	4	8	2	1	-	-	-
Proteus mirabilis	10	-	3	-	-	-	-	-
Staph aureus	4	2	-	1	2	1	-	-
Klebsiella oxytoca	4	-	-	-	-	-	-	-
Acinetobacter baumanii	2	-	-	1	-	-	-	-
Enterococci	2	-	-	-	-	-	-	-
Micrococci	-	-	1	-	-	-	-	-
M.tuberculosis	-	6	-	-	1	-	-	-
Leptospira icterohaemorrhagiae	-	-	-	1	-	-	-	-
FUNGI								
Candida albicans	13	1	4	-	-	1	10	-
Candida species	3	-	-	-	-	-	2	-
Aspergillus fumigatus	-	1	-	-	-	-	-	-
Aspergillus flavus	-	2	-	-	1	-	-	-
Mucor	-	1	-	-	-	-	-	-
T.rubrum	-	-	-	-	2	-	-	-
T.mentagrophytes	-	-	-	-	1	-	-	-
Cryptococcus	-	-	-	-	-	-	-	1
VIRUS	-	-	-	-	-	-	-	-
CMV	-	-	-	8	-	-	-	-
Hepatitis B	-	-	-	4	-	-	-	-
Hepatitis C	-	-	-	5	-	-	-	-
PARASITE								
Plasmodium falciparum & vivax	-	-	-	4	-	-	-	-
E.h cyst	-	-	-	-	-	-	3	-
A.duodenale	-	-	-	-	-	-	1	-
S,stercoralis	-	-	-	-	-	-	1	-

DISCUSSION

Successful renal transplantation is today's best chance for rehabilitating individuals with end stage renal disease. To achieve this goal, prevention and treatment of infectious disease complications of transplantation are of major importance and the requisite immunosuppressive therapy must be judiciously administered (Rubin,1993)9.

Eighty eight renal transplant recipients were included in the present study. It comprised of 60 consecutive renal transplant recipients, transplanted during Jan 2004 to Dec 2005 and 28 renal transplant recipients, transplanted before Jan 2004 and admitted for infection during Jan 2004 to Dec 2005 (Table 1).

The study group comprised of 79.5% male recipients and 20.5% of female recipients, male to female ratio being 3.8:1 (Table 2). In a study by Ravikumar (1992)83, there was a predominance of male population (82.5%) and male to female ratio of 4.7:1 during July 1987 to 1992. The predominant age group in this study was between 21 - 40 yrs (Table 2).

87 cases underwent Live donor transplantation and 1 case underwent Cadaver transplantation.

Total number of infectious episodes in this study were 246 (Table 3).

Urinary tract infections were common followed by Respiratory tract infections (Table 4).

Bacterial infections were the most common infections in the post transplant period (Table 5).

URINARY TRACT INFECTION

Urinary tract infections were the single most common infection occurring in renal transplant recipients, as noted in the present study and also reported by Rubin et al (1981)13 and Desai JD.S., Jadav et al (1992)84. Urinary tract infection constituted 52.8% (Table 4) of the total infectious episodes in the study. Desai JD.S., Jadav et al (1992)84 observed the incidence of 53% in their study, which coincides with this study. In studies carried out by Hinmanf (1969)17, Leigh D.A.(1970)18, Chan PC (1990)88 the reported incidence varies from 30- 79%. The incidence was found to be 51% by Ravi kumar(1998)83 in the study done in Government General Hospital, Chennai. 68% of the patients developed one or more urinary tract infections in this study as compared to 43% in a study by Chuang et al (2005)86.

45 patients (75%) had multiple episodes of infections and 15 patients(25%) had single episode of urinary tract infection. Mroz et al(1993)85 observed similar results in his study. Ravi kumar (1998)83 had a higher rate of single infections (60%) in his study. Increased incidence of urinary tract infections were noted in Males.

The aetiological agents causing urinary tract infection in the present study were Bacteria (87.6%) and Fungi (12.4%) (Table 7). The bacterial isolates included *E.coli, Klebsiella pneumoniae, Klebsiella oxytoca, Pseudomonas aeruginosa, Proteus mirabilis, Staph aureus, Acinetobacter baumanii* and *Enterococcus faecalis* (Table 7). Similar organisms were also isolated by Paul D. Ellner (1987)23. *E.coli* (39.4%) followed by *Klebsiella pneumoniae* (24.5%) were the most frequently isolated organism in this study. Takai et al (1998)29 found that *E.coli* was the commonest organism causing urinary tract infection. Gram negative bacilli of Enterobacteriaceae family were most frequently isolated in urinary tract infections in a study by Morz E et al (1993)85.

12.45% of the urinary tract infections were due to fungi of which 81.25% was due to *Candida albicans*, 12.5% were due to *Candida krusei* and 6.2% were due to *Candida tropicalis*. 87.5% of the urinary tract infections caused by *Candida* occurred within 6 months of renal transplantation(Table 8) as compared to 61.7% in a study by Moyses et al(1997)96. Funguria has been attributed in part to the widespread use of broad spectrum antibiotics, Corticosteroid, antineoplastic agents, immunosuppressive agents and urinary catheterization.

In the present study it was noted from the incidence of urinary tract infection in relation to post transplant duration, there was a decline in urinary tract infection after one month post transplant(Table 8). Mroz et al(1993)85 and Ravi kumar (1998)83 also observed the same in their study. The increased incidence of Urinary tract infections in the first month after transplant could be attributed partly to post surgical complications and partly due to immunosuppression.

RESPIRATORY TRACT INFECTION

Respiratory tract infection constituted about 10.3% of the total infectious episodes in the current study (Table 4). The reported incidence varies from 8% as observed by Moore F.D et al (1983)31, 15% by Giri (1992)82 and 12.6% by Ravi kumar (1998)83. The causative organisms were more commonly Bacterial (81.4%) and Fungal infections constituted 18.6% (Table 10).

Higher incidence of Respiratory tract infections were noted in males.(Table 9). Organisms causing bacterial infection were *Klebsiella pneumoniae* (45.4%), *Mycobacterium tuberculosis* (27%), *Pseudomonas aeruginosa* (18%) and *Staph aureus* constituted 9% of the bacterial infections. Similar organisms were isolated in other studies by Desai JD.S Jadav et al (1993)84 and Ravi kumar (1998)83.

Mycobacterium tuberculosis was isolated in 6 patients. Three were isolated from sputum, two were isolated from Bronchoalveolar lavage fluid and one was isolated from pleural fluid. The incidence of *Mycobacterium tuberculosis* was 27% among respiratory tract infections as compared with 37% in a study by Jha et al (1999)41. Most of the cases of *M.tuberculosis* occurred within one year post transplant (Table 11).

Gee-Chen Chang(2004)87 also reported pulmonary infections within one year post transplant. In a study by Lattes et al (1999)40, median time of onset of Tuberculosis was 13 months after renal transplantation.

Fungal infections constituted 18.6% of the total respiratory tract infections. The

incidence of 0-14% fungal infection was reported by Paya CV(1993)92 and Dummer et al (1983)93. The fungi isolated in this study were *Aspergillus flavus, Candida albicans, Aspergillus fumigatus* and *Mucor* (Table 10). Ravi kumar(1998)83 observed *Aspergillus flavus* and *Candida albicans* as the fungi causing respiratory tract infections in his study.

DRAIN INFECTION

Total number of drain infections was 23 (9.3%) (Table 4). Bacterial isolates were 19 and fungal isolates - 4. The Bacterial isolates included *Pseudomonas aeruginosa* (8), *E.coli* (4), *Staph aureus* (3), *Klebsiella pneumoniae* (3) and *Micrococci* (1). *Pseudomonas aeruginosa* was the predominant organism causing drain infection. The fungal isolates were *Candida albicans* (Table 12). Similar results were obtained by Ravi kumar in his study (1998)[83].

GASTROINTESTINAL TRACT INFECTION

Infections of the Gastrointestinal tract occurred in 6.9% of the total infectious episodes. Incidence of 5% was noted by Giri (1992)82. The causative organisms isolated were Fungi (70.5%) and parasites (29.5%) (Table 13). *Candida albicans, Candida tropicalis* and *Candida glabrata* were the fungi isolated.

E.h. cyst, Ankylostoma duodenale and Strongyloides stercoralis were the parasites found in the present study (Table 14). *Strongyloides stercoralis* was isolated in a patient who had a cadaver transplant. Majority of the GIT infections occurred between 2 – 6 months post transplant duration. Oral candidiasis was found in 43.75 % of the gastrointestinal tract infection in this study (Table 15) which correlated with 44%

observed in a study by Giri(1992)82.

BACTEREMIA

11episodes of bacteremia were noted in this study with organisms identified being *Klebsiella pneumoniae*-4*, Pseudomonas aeruginosa* - 2 *,E.coli*- 2, *Acinetobacter baumanii*-1*, Staph aureus* -1 *and Leptospira icterohaemorrhagia*-1 (Table 16). Out of 88 patients, 12.5 % developed Bacteremia in the present study compared with 11.5% of bacteremia observed by Moreno A (1994)98 in his study. *Klebsiella pneumoniae* were the commonest organism identified in the present study, but Lin et al(2001)56 reported *E.coli* being the commonest isolate.

SKIN AND SOFT TISSUE INFECTION

Skin and soft tissue infection accounted for 4% of the infectious episodes (Table 4). Among the 6 bacterial infections, *Staph aureus-2, E.coli*-2 and *Pseudomonas aeruginosa*-1 were isolated. *Mycobacterium tuberculosis* was isolated in one patient with lymphadenitis. Among the Fungal infections, *Trichophyton rubrum* was the commonest isolate (Table 17). Similar results was observed in a study by Thambiah et al (1999)62. Other fungi isolated were *Trichophyton mentagrophytes* and *Aspergillus flavus*.

CYTOMEGALOVIRAL INFECTION

Cytomegalovirus infection is a recognized problem of the early post transplant period in renal transplant recipients (Boehter A, 1994)99. In the present study, eight patients (3.2%) developed cytomegalovirus infection-5 patients developed *CMV* infection within 12 months of transplantation and 3 patients developed *CMV* infection after one year post transplant (Table 23).

VIRAL HEPATITIS

HEPATITIS C

Hepatitis C virus is the leading cause of post transplant Non A Non B hepatitis (Roth, 1991)73. 5.6 % of the patients tested positive for Anti-HCV antibodies by ELISA in this study. In a study by Yuan et al (2005)95, 5.8% of the patients were positive for Anti - HCV antibodies *Hepatitis C* infection occurred more commonly after one year post transplant (Table 19).

HEPATITIS B

1.6% of the total infectious episodes were caused by *Hepatitis B*. All the patients were positive for HBs Ag by ELISA. The HBs Ag positive individuals were preoperatively negative. Majority of the *Hepatitis B* cases occurred after one year post transplant (Table 20). In the study done by Ravi kumar (1998)83, 3.5% of the infectious episodes were caused by *Hepatitis B*.

WOUND INFECTION

The incidence of wound infection was 2.4% (Table 4) in the present study. The reported incidence varies from 0.7% by Kyriakides (1975)79, 4% by Desai JD.S.Jadav (1993)84, 1.3% by Giri(1992)82 and 2.2% by Ravi kumar (1998)83. Bacteria was isolated in 5 patients which included two *Klebsiella pneumoniae,* two *E.coli* and one *Staph aureus*. *Candida albicans* was isolated in one patient (Table 21). ajority of the wound infections occurred in the first one month post transplant period.

MALARIA

Malaria occurred in 4 patients and it constituted 1.6% of the total infectious episodes (Table 4). *Plasmodium falciparum* (2) and *Plasmodium vivax* (2) were the causative organisms. Two patients had malaria during the first month post operative period. Though 40% mortality in renal transplant recipients with

Plasmodium falciparum has been reported by Guecol I (1989)[64], no deaths have occurred due to malaria in the present study.

CENTRAL NERVOUS SYSTEM INFECTION

One patient developed meningitis which constituted 0.4% of the total infectious episodes (Table 4). Giri(1992)82 has reported the incidence of 0.7% in his study. The causative organism was found to be *Cryptococcus neoformans*. The patient developed meningitis in the 9th month post transplant. Ravi kumar (1998)83 also observed 2 cases of *Cryptococcus neoformans* meningitis in his study. It has been mentioned that *Cryptococcus neoformans*, the single most common cause of central nervous system

infection in the renal transplant patients, occurs almost exclusively in the late post transplant period (more than six months after transplant) Robert H. Rubin (1993) 9.

In the present study it was noted that infections in renal transplant patients were commonly caused by Bacteria(71.9%) followed by Fungi(17.4%), Viruses(6.9%) and Parasites(3.6%).

Bacterial, Fungal and Parasitic infections occurred most commonly within 6 months of renal transplantation. Viral infections occurred predominantly after 6 months of transplantation.

Urinary tract infections were the commonest cause of infection within one month post transplant period and it was 71.8% (Table 22) in this study. Ravi kumar (1998)83 observed the incidence of 68.5% of infections were due to urinary tract infection during the first one month post transplant period. 90% of the urinary tract infections occurred within one month post transplant was noted by Mroz E et al(1993)85 and it was 70% in the present study.

In the current study out of 88 patients,10 patients died, the mortality rate was 11.6% (Table 24). The single most common cause of death in this study was due to Bacteremia (40%). Ravi kumar (1998)83 observed a mortality rate of 22.5%, Bacteremia constituting 44.4% in his study.

ANTIBIOGRAM (Table 25, 26)

In this study, Gram positive organisms (*Staph aureus, Enterococcus fecalis, Micrococci*) were highly sensitive to Vancomycin (100%).

- *Staph aureus* showed 84.6% sensitivity to Oxacillin, 76.9% sensitivity to Erythromycin and 69.2% sensitivity to Ofloxacin. The 2 isolates that were resistant to oxacillin (MRSA) were sensitive to Vancomycin.

- *Enterococcus faecalis* showed 50% sensitivity to Ampicillin and Erythromycin.

- *Micrococci* was found to be 100% sensitive to Erythromycin and Ofloxacin.

All the Gram negative organisms isolated showed 100% sensitivity to Imipenem.

- *E.coli* was sensitive to Ceftazidime (96.2%), Cefaperazone(96.2%) followed by Ofloxacin (92%) and Ampicillin(79.2%).

- *Klebsiella sp* showed 100% sensitivity to Cefaperazone and Ceftazidime followed by 85% sensitivity to Gentamycin and Cefuroxime.

- *Pseudomonas aeruginosa* showed a sensitivity of 65.7% for Cefaperazone and Ceftazidime followed by 63.1% sensitivity to Gentamycin.

- *Proteus mirabilis* was found to be 100% sensitive to Cefaperazone, Ofloxacin and Ampicillin.

- *Acinetobacter baumannii* showed 100% sensitivity to Ceftazidime,

Cefaperazone, Ofloxacin and Gentamycin.

15 isolates (2 *E.coli* and 13 *Pseudomonas aeruginosa*) were found to be resistant to Third generation cephalosporin, Ceftazidime.

Among the 15 Ceftazidime resistant organisms, 11 isolates (2 *E.coli* and 9 *Pseudomonas aeruginosa*) tested positive for ESBL production.

MIC for Ceftazidime: 1 isolate (*E.coli*) had a MIC of 64 microgram/ml. 14 isolates (13 *Pseudomonas aeruginosa* & 1 *E.coli*) had MIC > 256 microgram/ ml.

Plasmid was extracted in 8 *Pseudomonas aeruginosa* isolates.

Table 27 shows isolation of Bacterial, Fungal, Viral and Parasitic infections in relation to the systems involved.

SUMMARY AND CONCLUSION

- Eighty eight renal transplant recipients were included in the present study.
- The predominant age group undergoing renal transplantation was between 21 - 40 yrs.
- There was a Male preponderance undergoing renal transplantation.
- Total number of infectious episodes in this study were 246.
- Urinary Tract infections (52.8%) were the commonest infection observed in this study. This was followed by Respiratory tract infection (10.3%), Drain infection (9.3%), Gastrointestinal tract infection (6.9%), Bacteremia (4.4%), Skin and soft tissue infection (4%), Hepatitis (3.6%), Cytomegalovirus infection (3.2%), Wound infection (2.4%), Malaria (1.6%), Central nervous system infection (0.4%).
- The microorganisms involved in the infections were Bacteria (71.9%), Fungus (17.4%), Virus (6.9%) and Parasite (3.6%).
- In Urinary tract infection, *E.coli* (39.4%) followed by *Klebsiella pneumoniae* (24.5%) were the predominant bacterial isolates. *Candida albicans* (81.2%) were the commonest fungus isolated.
- In Respiratory tract infections, *Klebsiella pneumoniae* (45.4%) and *Mycobacterium tuberculosis* (27%) were the most frequently isolated organisms. *Aspergillus flavus, Aspergillus fumigatus, Candida albicans* and *Mucor* were the fungi isolated.
- The majority of drain infections were caused by *Pseudomonas aeruginosa* followed by *E.coli* and *Candida albicans*.
- Among the Gastrointestinal tract infections, *Candida albicans* were the commonest fungal isolate. Parasites causing GIT infection included *Ankylostoma duodenale, Entamoeba histolytica cyst* and *Strongyloides*

stercoralis.

- *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the invasive bacteria causing Bacteremia in renal transplant recipients.

- Bacterial causes of Skin and soft tissue infections were *Staph aureus, E.coli, Pseudomonas aeruginosa and Mycobacterium tuberculosis*. *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Aspergillus flavus* constituted the fungal causes of Skin and soft tissue infections.

- Only 6 patients had wound infection. The organisms isolated were *Klebsiella sp, Staph aureus, E.coli* and *Candida albicans*.

- *Plasmodium falciparum* and *Plasmodium vivax* were involved as etiological agents causing infection in 4 patients.

- *Cryptococcus neoformans* was isolated in one case of meningitis.

- *Hepatitis B* (23.5%) and *Hepatitis C* (29.4%) were the organisms causing Viral Hepatitis.

- In the first one month post transplant period, the most common infection was Urinary tract infection (71.8%) followed by Drain infection (17.9%). Between 1 to 6 months post transplant duration, Urinary tract infections (40.9%) were predominant followed by Respiratory tract infections (21.3%).

- Infection by *Mycobacterium tuberculosis* occurred predominantly within one year post transplant duration.

- Viral infections (*Hepatitis B, Hepatitis C, CMV*) occurred predominantly after 6 months post transplant period.

- Gram positive bacteria showed 100% sensitivity to Vancomycin followed by Erythromycin.
- Gram negative bacteria were 100% sensitive to Imipenem followed by Cefaperazone. ESBL production was positive in 11 gram negative isolates.
- Plasmid was isolated in 8 Pseudomonas aeruginosa isolates.
- The mortality rate in this study was 11.6% of which Bacteremia constituted 40%.

It is clearly emphasized that early and correct recognition of infectious agents in renal transplant recipients during immediate and late post transplant period will improve the outcome of the patients.

In this study the organisms causing infection during the immediate and late post operative period has been categorized and the common sensitivity pattern has been analyzed, which will give the treating physician a reasonable idea to suspect the system and cause of infection during the particular post renal transplant period.

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